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SUBTITLE: Amelioration of Focal Epileptiform Activity Using a Topical (Cortical) Agent (Nimodipine) in a Porcine Model

PRINCIPAL INVESTIGATOR: William C. Bergman, COL, MC, USAR

CONTRACTING ORGANIZATION: Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, Maryland 20814-4799

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6. AUTHOR(S)
William C. Bergman, COL, MC
Leon E. Moores, MAJ, MC

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD, 20814-4799

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60-80 pound male pigs were subjected to general anesthesia, using a balanced narcotic technique (fentanyl). The animals were then subjected to removal of the entire flat surface of the calvarium, as well as the dura (aside from the superior sagittal sinus). A cortical electro-encephalographic (EEG) grid (PMT Corp.) was then placed over the surface of the exposed brain. Through a 3mm. hole in the grid, a seizure focus was established, using penicillin (5,000,000 U./cc.). Once this was definitively established, the penicillin was removed and replaced with a calcium channel blocker (nimodipine). In two out of four procedures, the focal epileptiform activity was ameliorated or altered.

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INTRODUCTION

Although the vast majority of patients with seizure disorders can be adequately managed with systemic (oral) anticonvulsant agents, a small but significant minority remain intractable to such measures. Some of these patients eventually require ablative surgery (resection of small volumes of brain tissue) in order to eventually control their seizures. The extent of resection in such surgical procedures is based on a combination of preoperative and intraoperative EEG monitoring, but the exact dimensions and limits of the brain to be resected, in order to effect the desired result yet not injure any needed brain, is, at best, less than exact. It would be highly beneficial to have a technique which would allow reversible seizure control which could be performed preoperatively, or even as a separate surgical procedure, prior to removing brain and creating a situation which, if the wrong judgment regarding dimensions is made, leaves the patient with either an inadequate resection or irreversible loss of function. A topical anticonvulsant agent (a substance which could be applied directly to the cortex) which could be delivered using a device, the components of which are already in existence, would be highly beneficial in this regard.

An additional benefit of such an agent would be its potential use in patients with open or penetrating head injuries. Such patients, which are all too commonly seen in the combat scenario, will have exposed brain, and are very likely to seize. This is even more likely if the patient has been exposed to certain chemical agents. The "golden opportunity" to most effectively and definitively control these seizures is as early as possible, potentially at the scene of the trauma. Although systemic anticonvulsant agents are commonly given at this point in this scenario, they are frequently inadequate to effect the desired results. A topical agent which could be applied directly to the cortex, in such a situation, might well be highly beneficial.

For the reasons described above, we are endeavoring to develop an agent which will control seizure activity when applied directly to the brain cortex surface.

Work by Lockard (1) suggests that a calcium channel blocker flunarizine applied directly to the cortex of Rhesus monkeys, which had been subjected to the development of an epileptic focus (using alumina gel) showed a significant diminution of the frequency and intensity of their seizures. Previous work by this author (2) suggests that a similar calcium channel blocker (nimodipine) will ameliorate focal epileptiform discharges, when applied directly to the cortex of pigs subjected to a penicillin focus. This latter work proved to be somewhat sporadically repeatable, suggesting that an optimal technique needed further development. To this end, we are endeavoring to improve and perfect this technique.

MATERIALS AND METHODS

60 to 80 lb. male (in order to avoid hormonal variations) pigs were subjected to general anesthesia, using a balanced narcotic (fentanyl) technique. The skin was incised in the mid-sagittal line along the entire A-P diameter of the calvarium. After hemostasis was achieved, the scalp was elevated away from the entire dorsal surface of the calvarium, and that bony structure was removed in its entirety. Again, hemostasis was achieved, and the exposed dura was then removed, bilaterally, except for the superior sagittal sinus. A 16-lead cortical EEG grid (PMT Corporation) was placed directly over the exposed brain, in such a manner that eight leads were present over the surface of cortex of each hemisphere. This was then connected to a standard electroencephalographic (EEG) recording device (Nicolet Corporation). Prior to its placement over the cortex, a 3mm hole was placed in the grid, through which various agents could be delivered.

After recording baseline tracings, a cotton pledget soaked in penicillin (5 million units per milliliter) was placed directly over the hole. The EEG tracing was observed for evidence of epileptiform electrical activity, and the pledget was removed as soon as the first spikes were noted. The cortex was irrigated, in order to remove all traces of penicillin, and the focus was allowed to develop. It was observed for approximately one-half hour, in order to ensure that the presence of the penicillin was no longer necessary.

A similar pledget, this time soaked in nimodipine (Nimotop R, Miles Pharmaceutical) was placed over the same hole. Results were then recorded.

At the end of the procedure, the animal was euthanatized by overdose.

RESULTS

Five subject animals were subjected to the described procedures. One procedure was aborted because the animal had a preexistent generalized seizure discharge noted when the grid was first applied. Of the remaining four, two developed seizure foci which expanded well beyond the limits of the focus of the cortex under the hole. Of the remaining two, one developed burst suppression following the application of the nimodipine. This took place in spite of the fact that the focus did not appear to be deteriorating. In the remaining subject animal, the epileptiform focus was significantly diminished in its amplitude and frequency of discharge after the application of the nimodipine.

CONCLUSIONS

1. The use of fentanyl, as opposed to the isofluorane used in the author's previous work (2), eliminated the presence of sporadic, preexistent spikes, which were a problem in the author's previous work.

2. Nimodipine ameliorates epileptiform activity generated by penicillin, but only if the epileptiform focus is limited to the area in direct contact with the nimodipine. This amelioration can be evidenced by either the diminution of epileptiform activity or the development of burst suppression.

3. Further work is necessary to show that these results can be repeated statistically.

REFERENCES

1. Lockard,J.S.; Levy,R.H.; Congdon,W.C.; McNabb,M.L.: Flunarizine Administered Focally Delays Epileptogenesis in an Experimental Model. Epilepsia 30, 5, 1989, 649.

2. Bergman,W.C.; Baker,J.T.; Vance,S.C.; Barbaro,N.M.; Gelinas-Sorell,D.; Brooks,D.E.; Fredericks,D.; Rodkey,W.G.: Cessation of Focal Seizure Activity Using Calcium Channel Blocker (nimodipine) Applied Directly to the Cortex. Poster presented to the Annual Conference of the American Association of Neurological Surgeons, April 1991.